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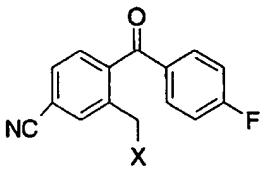
(54) Title: PROCESS FOR THE PREPARATION OF 1-(3-DIMETHYLAMINOPROPYL)-1-(4-FLUOROPHENYL)-1,3-DIHYDROISOBENZOFURAN-5-CARBONITRILE




(III)

(57) Abstract: Method for the preparation of 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (citalopram) comprising the reaction of a compound of formula (III) wherein X is a halogen, with organometallic dimethylaminopropyl halide. Other aspects of the invention are new compounds of formula (II) and formula (III) and their preparation.

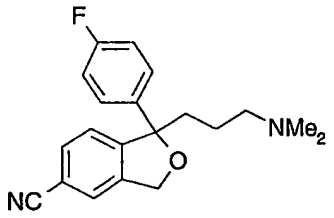
# PROCESS FOR THE PREPARATION OF 1-(3-DIMETHYLAMINOPROPYL)-1-(4-FLUOROPHENYL)-1,3-DIHYDROISOBENZOFURAN-5-CARBONITRILE

The present invention relates to a novel process for the preparation of 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, which is a well known antidepressant, citalopram.

## BACKGROUND OF THE INVENTION

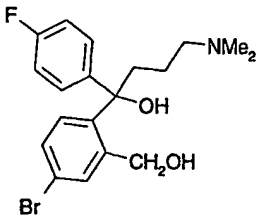
Citalopram is a selective, centrally acting serotonin (5-hydroxytryptamine; 5HT) reuptake inhibitor having antidepressant activity. This activity has been described e.g. in J. Hyttel, Prog. Neuro-Psychopharmacol. & Biol. Psychiat., 1982, 6, 277-295 and A. Gravem, Acta Psychiatr. Scand., 1987, 75, 478-486. In EP-A 474 580 it has been disclosed that citalopram has also effects in the treatment of dementia and cerebrovascular disorders.

Citalopram has the following structure:




I

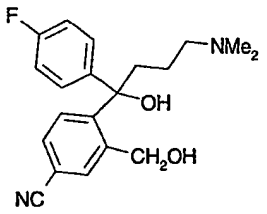
Citalopram was first described in DE 2,657,013 corresponding to US 4,136,193. It was prepared by the reaction of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile with a 3-(N,N-dimethylamino)propyl halide in the presence of a condensing agent. The starting material was prepared from the corresponding 5-bromo derivative by a reaction with cuprous cyanide. The other, in general terms outlined reaction comprises the ring closure of 5-bromo dihydroxy compound of formula IV




IV

in the presence of a dehydrating agent. After the ring closure the 5-bromo group is replaced by a cyano group using cuprous cyanide. The starting material for a compound of formula IV is obtained from 5-bromophthalide by two successive Grignard reactions.

Another preparation process is described in US 4,650,884. In that process the ring closure of dihydroxy compound of formula V

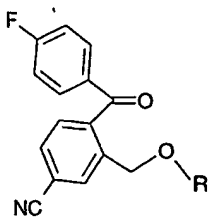



V

is achieved by dehydration with strong sulfuric acid. The starting material is prepared from 5-cyanophthalide by two successive Grignard reactions.

Other processes for the preparation of citalopram are disclosed in patent applications WO 98/19511, WO 98/19512, WO 98/19513, WO 99/30548, WO 2000/12044, WO 2000/13684 and WO 2000/23431. In US 4,943,590 preparation methods of individual enantiomers of citalopram are disclosed. In the process described dihydroxy compound of formula V is first transferred into an ester and ring closure is then achieved in the presence of a base.

In the process described in WO 2000/12044 ring closure of a compound of formula VI

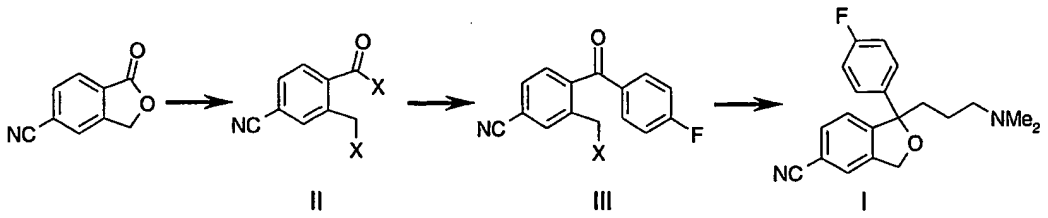



VI

takes place spontaneously after a reaction with 3-(N,N,-dimethylamino)-propyl magnesium halide. Three different ways to prepare compound VI are described. One of the methods includes protection of (4-cyano-2-hydroxymethylphenyl)-4-fluorophenyl methanol followed by an oxidation to afford compounds of formula VI. The starting hydroxymethyl alcohol compound can be obtained from a phthalide compound by a Grignard reaction followed by the reduction of the resulting ketone. Another method comprises the reaction of 5-cyanophthalide with 4-fluoromagnesiumhalide followed by the the reaction with R-X, wherein R is $C_{1-6}$ alkyl, acyl, alkylsulfonyl ar arylsulfonyl and X is a leaving group, to afford compound VI. In the reaction of 5-cyanophthalide also the resulting ketone compound can react with a Grignard reagent used and undesirable side products are formed. It is also possible that the product forms a cyclic hemiketal which does not react in the following step. The third preparation method for compound VI described in WO 00/12044 can be used for the preparation of S-enantiomer of citalopram.

## SUMMARY OF THE INVENTION

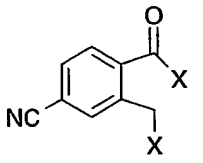
The present invention is directed to a novel process for the preparation of citalopram comprising halogenation of 5-cyanophthalide to afford an acid halogenide compound of formula II wherein X is a halogen, and threafter obtaining citalopram through two successive reactions with suitable organometallic halides or organoboranes according to scheme 1.




Scheme 1

The process comprises:

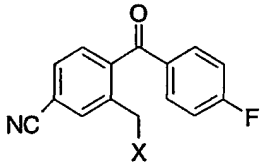
a) halogenation of 5-cyanophthalide, thereby obtaining a compound of formula II




II

wherein X is halogen,

b) the reaction of a compound of formula II with an organometallic 4-fluorophenyl halide or 4-fluorophenylborane to afford a compound of formula III




III

wherein X is as defined above, and

c) the reaction of a compound of formula III with organometallic dimethylaminopropyl halide to afford 1-(3- dimethylamino-propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (citalopram), which is isolated as the base or a pharmaceutically acceptable salt thereof.

Formation of halide compound of formula II serves twofold. High selectivity of the following reaction is obtained and a leaving group in the benzylic position is

introduced, so that ring closure to citalopram occurs spontaneously after treatment with a second Grignard reagent.

Resulting citalopram is isolated as the base or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention are novel intermediate compounds of formula II and III wherein X is a halogen, preferably chloro or bromo, most preferably chloro.

Still other aspects of the invention are processes for the preparation of said intermediates of formula II and III.

Yet another aspect of the invention relates to an antidepressant pharmaceutical composition comprising citalopram or its pharmaceutically acceptable acid addition salts prepared by the process of the invention.

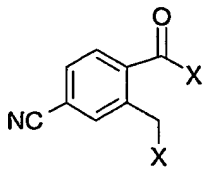
Halogen means chloro, bromo, iodo or fluoro.

The process of the present invention from 5-cyanophthalide to citalopram via acid halogenide is not described in any of the patents mentioned or in any other publication known.

DETAILED DESCRIPTION OF THE INVENTION

Surprisingly, it has been found that if 5-cyanophthalide is halogenated, the reaction of the resulting compound of formula II with an organometallic 4-fluorohalide or with a 4-fluorophenyl borane is very selective and the following reaction of a compound of formula III with organometallic 3-dimethylaminopropyl halide gives citalopram in good yield and purity.

The first step of the process is the halogenation of 1-oxo-1,3-dihydro-isobenzofuran-5-carbonitrile (5-cyanophthalide) to form the compound of formula II where X is halogen, preferably chloro or bromo, most preferably chloro.



II

The halogenation can be performed by any suitable method known in the art, eg. by the reaction with thionyl chloride in the presence of a suitable Lewis acid catalyst and a phase transfer catalyst. Catalysis by N,N-dimethylformamide (DMF) is also possible. Suitable Lewis acid catalysts are e.g. $MgCl_2$, $MgBr_2$, $SnCl_2$, $SnCl_4$, $ZnCl_2$, $TiCl_4$, $AlCl_3$, $FeCl_3$, $BF_3Et_2O$, $BF_3$, $BBr_3$, $BCl_3$, $B(OEt)_3$, $B(OMe)_3$, $B(O\text{-}iPr)_3$, preferably a boron based Lewis acid catalyst is used. Types of phase transfer catalyst used are halides of aromatic or aliphatic ammonium salts, for example tetramethyl-ammonium chloride, tetrabutylammonium chloride or benzyl triethylammonium chloride, or phosphonium salts, for example butyltriphenylphosphonium chloride or tetraphenylphosphonium chloride. Catalysts are used 0.1 to 20 mol % each, preferably 0.5 to 10 mol %. The reaction with catalysts can be performed without any solvent, but if a solvent is used, any inert, high boiling solvent such as toluene, xylene, chlorobenzene or dichlorobenzene can be used.

The halogenation reagent used can be any suitable reagent used for halogenation, e.g. thionyl chloride, $PCl_3$, $PCl_5$, $CCl_4$ in triphenyl phosphine, oxalyl chloride or cyanuric chloride in trialkyl amine.

The reagents for preparing corresponding bromo compounds can be e.g. $PBr_3$, $PBr_5$, $PPh_3Br_2$, thionyl bromide or oxalyl bromide.

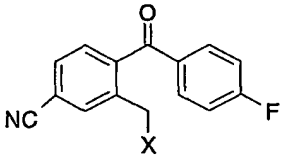
The halogenation reagent is used in the range from 0.5 to 1000 equivalents to cyanophthalide, preferably 1 to 10 equivalents, most preferably 1 to 5 equivalents. Reaction temperature can be from 20 to 150° C or reflux temperature, preferably 80 to 140° C, most preferably 100 to 130 ° C. The reaction time is from 0.5 to 15 h, preferably below 3 h.

The reaction will be completed readily and conversion is close to 100 %. The product can be isolated and purified by suitable methods known in the art or the following step can be performed without purification of compound II. The starting

material, 5-cyanophthalide, can be prepared e.g. as described in Tirouflet, Bull. Soc. Sci.Bretagne, 26, 1951, 35-46.

The advantage of making the acid halogenide is that the following reaction with an organometallic 4-fluorophenyl halide or with 4-fluorophenyl borane is very selective unlike the reaction of the lactone directly with 4-fluorophenylmagnesium halide, where the resulting ketone compound is more reactive than lactone and undesirable side products are formed.

The second step comprises the reaction of the halide compound of formula II with an organometallic or organoboron reagent to afford the compound of formula III.




III

The reagent used is a 4-fluorophenylborane or an organometallic 4-fluorophenyl halide, wherein the metallic component can be Mg, Li, Cu, or Zn, preferably Mg or Cu. Preferably the reagent is a 4-fluorophenylmagnesium halide or a Grignard reagent of a 1-halide substituted 4-fluorobenzene, wherein the halogen component is preferably Cl or Br. Most preferably 4-fluorophenylmagnesium bromide is used. The amount of the reagent used is from 0.5 to 2.5 equivalents, preferably from 1 to 1.5 equivalents.

The reaction is carried out in an inert organic solvent such as toluene, xylene or commonly used ethers such as tetrahydrofuran, diethylether, di-n-butylether, tetrabutylmethyl ether, ethylene glycol dimethyl ether, 1,4-dioxane or mixtures thereof. The preferred solvents are tetrahydrofuran and ethylene glycol dimethyl ether or their mixtures with toluene. Cu, Ni, Pd, Ti, Fe or Zn compounds can be used as catalysts, preferably the reaction is performed without any catalyst. Reaction temperature is -80 to 60° C, preferably -20 to 20° C. The reaction is selective and the resulting 4-(4-fluorobenzoyl)-2-halomethyl benzonitrile can be isolated and purified by crystallization or any other suitable method known in the art. The

following reaction can also be performed without isolation of the intermediate of formula III.

The final step is the reaction of compound III with an organometallic 3-dimethylaminopropyl halide whereafter the ring closes spontaneously to afford citalopram. The metallo component of the organometallic 3-dimethylaminopropyl halide reagent used can be Mg, Li, Cu, or Zn, preferably Mg or Cu, most prefereably Mg. Preferably the reagent is a Grignard reagent of a 3-(N,N-dimethylamino)propyl halide, wherein the halide is Cl or Br. Most preferably the reagent is 3-(N,N-dimethylamino)propylmagnesium chloride. The reaction is carried out in an inert organic solvent such as toluene, xylene or commonly used ethers such as tetrahydrofuran, diethylether, di-n-butylether, tetrabutylmethyl ether, ethylene glycol dimethyl ether or 1,4-dioxane or mixtures thereof. The preferred solvents are tetrahydrofuran or ethylene glycol dimethyl ether or their mixtures with toluene. Cu, Ni, Pd, Ti, Fe or Zn compounds can be used as catalysts, preferably the reaction is performed without any catalyst. Reaction temperature is -80 to 60° C, preferably -20 to 20° C and the reaction time is from 0.5 to 15 h, preferably below 3 h. The organometallic reagent is used from 0.5 to 2.5 equivalents, preferably from 0.8 to 1.8 equivalents.

After the reaction the ring closes spontaneously affording citalopram. The resulting citalopram can be isolated as a base or a pharmaceutically acceptable salt thereof.

All the reactions from 5-cyanophthalide to citalopram can be performed in one pot which makes the process convenient and saves costs and labour when no isolation or purification processes of intermediates are needed. Another method is to isolate compound II and then perform the following reactions b) and c) in the same pot without the separation of intermediates.

The compound of formula I may be used as a free base or as a pharmaceutically acceptable acid addition salt thereof. The acid addition salts can be prepared by methods known in the art.

The following examples merely illustrate the invention and they are not to be construed as limiting.

EXAMPLE 1.

2-Chloromethyl-4-cyano-benzoyl chloride:

1-Oxo-1,3-dihydro-isobenzofuran-5-carbonitrile (25 g), boron trifluoride etherate (0.8ml) and benzyl triethyl ammonium chloride (0.72g) were suspended in thionyl chloride (92 ml) and heated to reflux for 17 hours. Excess of thionyl chloride was distilled off under nitrogen to give an internal temperature of 95° C and heating to reflux was continued for another 24 hours. The product was purified by distillation under reduced pressure. Yield: 27.5 g, 92%. Melting point 44 -44.5 C. $^1$H NMR (CDCl3, 400MHz): 4.83 (2H, s), 7.74 (1H, dd, J = 1, 8 Hz), 7.89 (1H, d, J = 1 Hz), 8.25 (1H, d, J = 8 Hz). $^{13}$C NMR (CDCl3, 100MHz): 42.7, 116.8, 118.0, 132.2, 133.8, 134.0, 135.7, 140.0, 166.9. IR (KBr): • 3108, 3077, 2963, 2239, 1755, 1604, 1298, 1195, 1103, 944, 935, 840 cm$^{-1}$.

3-Chloromethyl-4-(4-fluoro-benzoyl)-benzonitrile:

A solution of 4-fluoro phenylmagnesium bromide (3.76 g) in tetrahydrofuran (15ml) was added to a cooled solution of 2-chloromethyl-4-cyano-benzoyl chloride (3.95 g) in tetrahydrofuran (10ml) so that the temperature did not raise above 0° C. The mixture was warmed slowly to room temperature and stirred over night. Saturated ammonium chloride solution (60 ml) was added and stirring continued for 0.5 hours. The phases were separated and the aqueous phase was extracted with diethylether (30ml). The combined organic phases were dried over sodium sulfate, filtered and dried *in vacuo* to give a brown solid. Flash chromatography (ethyl acetate/n-hexane = 1/10) provided the product as colourless solid. Yield 2.95g, 58%. $^1$H NMR (CDCl3, 400MHz): 4.71 (2H, s), 7.16-7.21 (2H, m), 7.46 (1H, d, J = 7.9 Hz), 7.71 (1H, dd, J = 1.5, 7.9 Hz), 7.81-7.86 (2H, m), 7.89 (1H, d, J = 1.5 Hz). $^{13}$C NMR (CDCl3, 100MHz): 42.3, 115.0, 116.4, 116.6, 117.9, 129.6, 132.95, 132.98, 133.4, 133.5, 134.3, 138.7, 142.4, 165.5, 168.1, 194.5.

1-(3-Dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile:

A solution of freshly prepared 3-dimethylaminopropylmagnesium chloride (0.6M in THF, 7.6 ml) was added to a cooled solution of 3-chloromethyl-4-(4-fluoro-benzoyl)-benzonitrile (0.5g) in ethylene glycol dimethyl ether (4ml) so that

the temperature did not raise above -4° C. The mixture was stirred for 30 minutes at –15° C and 100 minutes at room temperature before 0.5N hydrobromic acid was added to adjust the pH to 10. The phases were separated and the aqueous phase was extracted twice with toluene (25ml). The combined organic phases were dried over sodium sulfate, filtered and dried *in vacuo* to give a viscous oil (0.44g, 75 %). Spectral and analytical data were in accordance with the literature.

EXAMPLE 2.

2-Chloromethyl-4-cyano-benzoyl chloride:

1-Oxo-1,3-dihydro-isobenzofuran-5-carbonitrile (80 g), boron trifluoride etherate (4,4 ml), benzyltriethyl ammonium chloride (9,2g) and thionyl chloride (55 ml) were suspended in xylene (320ml). The mixture was heated to reflux for 4 hours and volatiles were removed under reduced pressure. The product was purified by distillation under high vacuum. Yield: 78,2g, 73%. Melting point 44 -44.5° C. $^{1}H$ NMR (CDCl3, 400MHz): 4.83 (2H, s), 7.74 (1H, dd, J = 1, 8 Hz), 7.89 (1H, d, J = 1 Hz), 8.25 (1H, d, J = 8 Hz). $^{13}C$ NMR (CDCl3, 100MHz): 42.7, 116.8, 118.0, 132.2, 133.8, 134.0, 135.7, 140.0, 166.9. IR (KBr): υ 3108, 3077, 2963, 2239, 1755, 1604, 1298, 1195, 1103, 944, 935, 840 $cm^{-1}$.

3-Chloromethyl-4-(4-fluoro-benzoyl)-benzonitrile:

A solution of 4-fluoro phenylmagnesium bromide (0.73M in THF, 170 ml) was added to a cooled solution of 2-chloromethyl-4-cyano-benzoyl chloride (25.0 g) in toluene (200 ml) so that the temperature did not raise above 0° C. The mixture was stirred at 0 °C for 2 hours. An aqueous solution of HCl (250 ml) was added and stirring continued for 0.5 hours. The phases were separated and the aqueous phase was extracted with toluene (200 ml). The combined organic phases were washed with saturated $NaHCO_3$ solution (200 ml) and water (100 ml). The solvents were evaporated *in vacuo* to give a brownish oil (29.0 g, 90 %). Spectral and analytical data were in accordance with the example above.

1-(3-Dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile:

A solution of 3-dimethylaminopropylmagnesium chloride (1.2M in THF, 84 ml) was added to a cooled solution of 3-chloromethyl-4-(4-fluoro-benzoyl)-benzonitrile (25.0 g) in a mixture of toluene (175 ml) and THF (50 ml) so that the temperature did not raise above -5° C. The mixture was stirred for 2 hours at 0 °C before water (100 ml) and saturated $NH_4Cl$ solution were added to adjust the pH to 9. The phases were separated and the aqueous phase was extracted twice with toluene (200 ml). The combined organic phases were washed with water (200 ml) and concentrated *in vacuo* to give a viscous oil (28,0 g, 95 %).
Spectral and analytical data were in accordance with the literature.

EXAMPLE 3.

1-(3-Dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile in one pot

1-Oxo-1,3-dihydro-isobenzofuran-5-carbonitrile (5 g), boron trifluoride etherate (0.2ml) and benzyl triethyl ammonium chloride (0.36g) were suspended in thionyl chloride (18 ml) and heated to reflux for 6 hours. Excess of thionyl chloride was distilled off under nitrogen and heating to reflux was continued for another 17 hours. Toluene (50 ml) was added and volatiles (45 ml) were distilled off. Dry tetrahydrofuran (25ml) was added and 4-fluorophenylmagnesium bromide (6.26 g) in dry tetrahydrofuran (25 ml) was added slowly at –15° C. The reaction mixture was stirred at room temperature for 3 hours and 3-dimethylamino propyl magnesium chloride (4.36 g) in dry tetrahydrofuran (20 ml) was added slowly at –15° C. The reaction mixture was stirred at room temperature over night and heated to reflux for 1 hour. The reaction was quenched with saturated ammonium chloride solution (300 ml) and the phases separated. The aqueous phase was extracted 3 times with *tert*-butyl methyl ether (100ml) and the combined organic phases were washed with brine (100 ml) and dried over sodium sulfate. Filtration and evaporation of volutiles gave a brown oil, which was dissolved in 1N hydrochloric acid (250 ml) and toluene (150 ml). The phases were separated and the organic phase was washed with 1N hydrochloric acid (100ml). The combined aqueous phases were treated with concentrated sodium hydroxide solution to obtain a pH of 14. The mixture was extracted 3 times with toluene (100ml) and the combined organic phases were washed with brine (100 ml) and dried over sodium sulfate. Filtration and evaporation

of volatiles gave a brown oil. Yield: 1 g, 10%. Spectral and analytical data were in accordance with the literature.

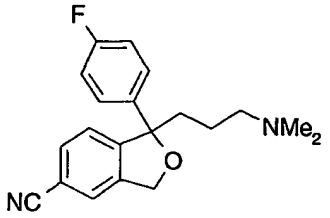
EXAMPLE 4.

1-(3-Dimethylamino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile:

A solution of 4-fluoro phenylmagnesium bromide (0.7M in THF, 16 ml) was added to a cooled solution of 2-chloromethyl-4-cyano-benzoyl chloride (1,75 g) in toluene (20 ml) so that the temperature did not rise above 0° C. After 40 minutes a solution of 3-dimethylaminopropylmagnesium chloride (0,85M in THF, 10 ml) was added so that the temperature did not rise above 2° C. The mixture was stirred for 30 minutes and water (30ml) was added. The pH of the mixture was adjusted to 4.5 and the phases were separated. The pH of the aqueous phase was adjusted to 8 and extracted with toluene (30ml) and 2-propanol (10ml). The organic phase was concentrated *in vacuo* to give a viscous oil (1,5 g, 56%). Spectral and analytical data were in accordance with the literature.

CLAIMS

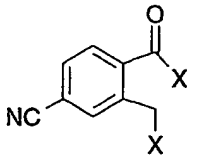
1. A method for the preparation of 1-(3-dimethylaminopropyl)-1-(4-fluoro-phenyl)-1,3-dihydroisobenzofuran-5-carbonitrile of formula I




I

comprising the steps:

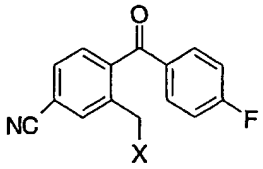
a) halogenation of 5-cyanophtalide, thereby obtaining a compound of formula II




II

wherein X is halogen,

b) the reaction of a compound of formula II with an organometallic 4-fluorophenyl halide or 4-fluorophenylborane to afford a compound of formula III




III

wherein X is as defined above, and

c) the reaction of a compound of formula III with organometallic dimethylaminopropyl halide to afford 1-(3- dimethylamino-propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (citalopram), which is isolated as the base or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein the organometallic 4-fluorophenyl halide in step b) is a Grignard reagent.

3. The method of claim 1 or 2 wherein the Grignard reagent in step b) is 4-fluorophenyl magnesium bromide.

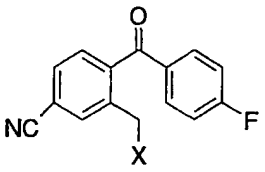
4. The method of any of claims 1-3 wherein the organometallic dimethylaminopropyl halide in step c) is a Grignard reagent.

5. The method of any of claims 1-4 wherein the the Grignard reagent in step c) is 3-(N,N-dimethylamino)propylmagnesium chloride.

6. The method of any of claims1 - 5 where X is Cl or Br.

7. The method of any of claims 1- 6 where X is Cl.

8. A compound having formula III



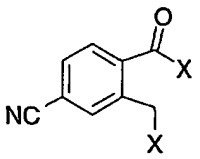

III

wherein X is halogen.

9. The compound of claim 8 wherein X is I, Cl or Br.

10. The compound of claim 8 or 9 where X is Cl.

11. A compound having formula II




II

wherein X is halogen.

12. The compound of claim 11 where X is Cl or Br.

13. The compound of claim 11 or 12 where X is Cl.

14. A method for the preparation of the compound of formula I comprising the reaction of a compound of formula III wherein X is a halogen, with an organometallic 3-dimethylaminopropyl halide.

15. A method of claim 14 wherein the organometallic 3 dimethylaminopropyl halide is 3-(N,N-dimethylamino)propylmagnesium chloride.

16. A method of claim 14 or 15 wherein X is I, Cl or Br.

17. A method of any of claims 14 to 16 wherein the compound of formula III is (4-fluorophenyl)-(2-chloromethyl-4-cyanophenyl)methanone.

18. A pharmaceutical composition comprising citalopram manufactured by the process of any of claims 1 to 7 or 14 to 17.

19. The method of any of the claims 1 to 7 which is performed in one pot without the separation of intermediates.

20. The method of any of claims 1 to 7 wherein reactions b) and c) are performed in one pot without the separation of intermediates.

21. A method for the manufacture of compound of formula III comprising the reaction of a compound of formula II with a 4-fluorophenylborane or with 4-fluorophenylmetallo halide.

22. A method for the manufacture of compound of formula II comprising the halogenation of 5-cyanophtalide.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 02/00064

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/87
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 28 March 2002 | 29. 05. 2002 |

| Name and mailing address of the International Searching Authority | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Göran Karlsson/BS<br>Telephone No. |

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Information on patent family members

28/01/02

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